Sponsor: Novartis Vaccines and Diagnostics S.r.l.

Investigational Product: Trivalent influenza virus vaccine (surface antigen, inactivated, egg-derived)

Indication: Prophylaxis: Influenza

Protocol Number: V71P7S

Protocol Title: A Phase II, Open Label, Uncontrolled, Multi Center Study to Evaluate Safety and Immunogenicity of AGRIPPAL S1 Surface Antigen, Inactivated, Influenza Vaccine, Formulation 2008-2009, when Administered to Non-elderly Adult and Elderly Subjects

Phase of Development: II

Study Period:

Date of first enrolment: 20 JUN 08

Date of last visit: 15 JUL 08

Methodology:

All subjects were to receive a single injection of subunit influenza vaccine on Day 0. Blood samples for the determination of antibody titers were drawn on Day 0 prior to vaccination and on Day 21 (-1/ +5). Subjects were observed at the clinic for 30 minutes after vaccination for any immediate reactions. Each subject was instructed to fill in a diary card for 3 days following vaccination to collect local (ecchymosis, erythema, induration, swelling, and pain) and systemic (chills/shivering, malaise, myalgia, arthralgia, headache, sweating, fatigue, and fever [i.e., axillary temperature ≥ 38°C]) reactions. Subjects were contacted by phone on Day 4 after vaccination to ensure that local and systemic reaction data had been collected on the Subject's Diary Card and also to determine the subject's clinical status. All adverse events (AEs; solicited and unsolicited) were collected during Day 0 to 3. All serious adverse events (SAEs) and/or AEs necessitating a physician's visit or consultation and/or resulting in premature subject's withdrawal from the study were collected throughout the study. Subjects were informed that in the event of severe inter-current infection they had to contact the Investigator who would take a nasal and/or pharyngeal swab to diagnose influenza or other respiratory infection of viral origin.

Number of Subjects (planned and analyzed):

A total of 126 subjects were planned to be enrolled, of which 63 in the non-elderly adult age group (age 18 to 60 years) and 63 in the elderly age group (age 61 years and above). This sample size allowed for 13 non-evaluable subjects. In the non-elderly adult age

group, no more than approximately half of the subjects should have been aged between 41 and 60 years.
A total of 133 subjects were actually enrolled. Of this total, 131 subjects were included in the safety analysis and 128 subjects in the immunogenicity analysis (Per Protocol [PP] set).

Study Centers:

Three centers in Italy.

Publication (reference) and/or ClinicalTrials.gov National Clinical Trial (NCT) Number:

NCT00748813

Objectives:

Immunogenicity Objectives: To evaluate the antibody response to each influenza vaccine antigen, as measured by Single Radial Hemolysis (SRH) at 21 days post-immunization in non-elderly adult and elderly subjects in compliance with the requirements of the current European Union (EU) recommendations for clinical trials related to yearly licensing of influenza vaccines. Antibodies may be additionally quantified using the hemagglutination inhibition test for confirmation purposes. (Note for Guidance on Harmonisation of Requirements for Influenza Vaccines. Committee for Proprietary Medicinal Products [CPMP]/BWP/214/96: 12 March 1997)

Safety Objectives: To evaluate safety of a single intramuscular (IM) injection of AGRIPPAL S1 in non-elderly adult and elderly subjects in compliance with the requirements of the current EU recommendations for clinical trials related to yearly licensing of influenza vaccine (CPMP/BWP/214/96).

Test Product, Dose, Mode of Administration, Lot Number:

AGRIPPAL® S1, influenza subunit vaccine for the Northern Hemisphere influenza season 2008/2009 was IM administered). Lot number: Y51P88H1.

Duration of Study:

Approximately 4 weeks (approximately 1 week enrollment, 3 weeks participation per subject).

Reference Therapy, Dose, Mode of Administration, Lot Number:

None.

Statistical Methods:

There was no statistical null hypothesis to be tested in this study. Statistical analysis was done descriptively.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Subjects eligible for enrollment into this study were male and female adults who were: ≥ 18 years of age, mentally competent, willing and able to give informed consent prior to study entry; able to comply with all study requirements and in good health as determined by medical history, physical examination and clinical judgment of the Investigator. Written informed consent had to be obtained from all the subjects before enrollment in the study after the nature of the study was explained.

Criteria for Evaluation:

Immunogenicity: Immunogenicity analyses were performed by SRH assay and assessed according to CPMP/BWP/214/96. In adult subjects aged 18 to 60 years at least one of the assessments was to meet the indicated requirements (CPMP/BWP/214/96) for each strain: i.e., seroprotection rate > 70%; seroconversion rate > 40%; post-/pre-vaccination geometric mean ratio (GMR) > 2.5. In elderly subjects aged 61 years and over at least one of the following assessments was to meet the indicated requirements (CPMP/BWP/214/96) for each strain: i.e., seroprotection rate > 60%; seroconversion rate > 30%; post/pre-vaccination GMR > 2.0.

Safety: Safety was assessed in accordance with available safety data on influenza vaccines. The incidence of local reactions and systemic reactions (Days 0 to 3) was summarized by maximal severity and by age group. The incidence of AEs (including local and systemic reactions with duration beyond Day 3 post vaccination) between Day 0 and the study termination visit was summarized by each age group and by preferred term and system organ class.

Results:

Table 1 Overview of Subject Populations

	Number (%) of Subjects		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
Population:			
Enrolled	67 (100%)	66 (100%)	133 (100%)
Immunogenicity (FAS)	67 (100%)	66 (100%)	133 (100%)
Immunogenicity (PP)	64 (96%)	64 (97%)	128 (96%)
Safety	66 (99%)	65 (98%)	131 (98%)

Abbreviations: FAS, Full Analysis Set; PP, Per Protocol; YOA, years of age.

Table 2 Summary of Study Terminations – All Enrolled Set

	Number (%) of Subjects		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
Enrolled	67	66	133
Completed protocol	64 (96%)	65 (98%)	129 (97%)
Premature withdrawals	3 (4%)	1 (2%)	4 (3%)
Withdrawal of consent	1 (1%)	0	1 (<1%)
Lost to follow-up	1 (1%)	1 (2%)	2 (2%)
Unable to classify	1 (1%)	0	1 (<1%)

Abbreviation: YOA, years of age.

Table 3 Demographic and Other Baseline Characteristics - All Enrolled Set

	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N = 67	**N = 66**	**N = 133**
Age (years):	45.5 ± 10.1	69.4 ± 6.5	57.3 ± 14.7
Gender:			
Male	29 (43%)	30 (45%)	59 (44%)
Female	38 (57%)	36 (55%)	74 (56%)
Ethnic origin:			
Caucasian	66 (99%)	66 (100%)	132 (99%)
Hispanic	1 (1%)	0	1 (<1%)
Weight (kg):	73.40 ± 13	72.06 ± 13.39	72.73 ± 13.16
Height (cm):	167.6 ± 8	165.2 ± 6.9	166.4 ± 7.5
Body mass index: (kg/m²)	26.0 ± 3.3	26.3 ± 4.1	26.1 ± 3.7
Previous influenza vaccination	39 (58%)	59 (89%)	98 (74%)

Abbreviation: YOA, years of age.
Categorical parameters: number (%) of subjects; non-categorical parameters: mean ± standard deviation.

Table 4 Vaccine Immunogenicity Assessed by SRH Test Using Egg-Derived Test Antigens – Per Protocol Set

		18-60 YOA (N=64)							≥ 61 YOA (N=64)						
Strains		**A(H1N1)**		**A(H3N2)**		**B**			**A(H1N1)**		**A(H3N2)**		**B**		
PREVACCINATION (Day 0)															
		n/N[1]	**%**	**n/N[1]**	**%**	**n/N[1]**	**%**		**n/N[1]**	**%**	**n/N[1]**	**%**	**n/N[1]**	**%**	
GMA[2]		14		6.93		10			25		8.32		12		
95% CI[3]		10-19		5.49-8.73		7.66-13			19-32		6.38-11		9.14-16		
Seroprotection rate[4]		29/64	45%	12/64	19%	21/64	33%		48/64	75%	14/64	22%	25/64	39%	
95% CI		33-58		10-30		22-46			63-85		13-34		27-52		
POSTVACCINATION (Day 21)															
	CHMP*	**n/N[1]**	**%**	**n/N[1]**	**%**	**n/N[1]**	**%**	**CHMP***	**n/N[1]**	**%**	**n/N[1]**	**%**	**n/N[1]**	**%**	
Seroconversion rate[5]		27/31	87%	29/46	63%	23/36	64%		11/14	79%	29/41	71%	18/31	58%	
Significant increase in antibody titres[6]		11/33	33%	9/18	50%	10/28	36%		10/50	20%	8/23	35%	7/33	21%	
Seroconversion rate or significant increase	**>40%**	38/64	**59%**	38/64	**59%**	33/64	**52%**	**>30%**	21/64	**33%**	37/64	**58%**	25/64	**39%**	
95% CI[3]		46-71		46-71		39-64			22-46		45-70		27-52		
GMA[2]		51		26		30			44		34		28		
95% CI[3]		43-61		19-35		23-40			38-51		26-44		22-36		
GM Increase	**>2.5**	**3.72**		**3.7**		**2.97**		**>2.0**	1.77		**4.05**		**2.28**		
95% CI[3]		2.74-5.05		2.69-5.09		2.18-4.06			1.4-2.24		2.92-5.62		1.72-3.02		
Seroprotection rate[4]	**>70%**	60/64	**94%**	45/64	70%	48/64	**75%**	**>60%**	60/64	**94%**	48/64	**75%**	46/64	**72%**	
95% CI[3]		85-98		58-81		63-85			85-98		63-85		59-82		

Abbreviations: CHMP, Committee for Proprietary Medicinal Products; GM, geometric mean; SRH, Single Radial Hemolysis; YOA = years of age.;
[1] n/N: responders (n) as part of number of subjects of the (sub-)population (N); [2] GMA: geometric mean area; [3] 95% CI: 95% confidence interval; [4] Seroprotection rate: proportion of subjects with a pre- or post-vaccination area $\geq$ 25 mm^2; [5] Seroconversion: proportion of subjects with negative pre-vaccination serum and a postvaccination serum area $\geq$ 25 mm^2; [6] Significant increase: proportion of subjects with at least a 50% increase in area from positive pre-vaccination serum.
* CHMP Criteria.
Bold values: CHMP criteria were met.

Table 5 Overview of Solicited Reactions – Safety Set

	Number (%) of Subjects With at Least One Solicited Reaction		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N=66	**N=65**	**N=131**
Any	19 (29)	17 (26)	36 (27)
Local	15 (23)	14 (22)	29 (22)
Systemic	6 (9)	8 (12)	14 (11)

Abbreviation: YOA, years of age.
Reactions with a diameter < 10 mm are considered as none for this summary.

Table 6 Overview of Solicited Local Reactions (0-3 Days Post-vaccination) – Safety Set

		Number (%) of Subjects With Injection Site Reactions		
		18-60 YOA	**≥ 61 YOA**	**TOTAL**
		N=66	**N=65**	**N=131**
Ecchymosis (mm)	Any	2 (3)	5 (8)	7 (5)
	> 50 mm	0	1 (2)	1 (1)
Erythema (mm)	Any	8 (12)	6 (9)	14 (11)
	> 50 mm	0	2 (3)	2 (2)
Induration (mm)	Any	6 (9)	5 (8)	11 (8)
	> 50 mm	0	1 (2)	1 (1)
Swelling (mm)	Any	2 (3)	3 (5)	5 (4)
	> 50 mm	0	1 (2)	1 (1)
Pain	Any	10 (15)	7 (11)	17 (13)
	Severe	1 (2)	0	1 (1)

Abbreviation: YOA, years of age.
Note: The numbers (N) in the header is the total number of subjects with documented reactions.
Categorization of Erythema, Swelling, Ecchymosis and Induration: none (diameter < 10 mm), mild (diameter 10-25 mm), moderate (diameter 26-50 mm) and severe (diameter > 50 mm).

Table 7 Overview of Solicited Systemic Reactions (0-3 Days Post-vaccination) – Safety Set

		Number (%) of Subjects With Systemic Reactions		
		18-60 YOA	**≥ 61 YOA**	**TOTAL**
		N=66	**N=65**	**N=131**
Chills / Shivering	Any	1 (2)	2 (3)	3 (2)
	Severe	0	0	0
Malaise	Any	0	2 (3)	2 (2)
	Severe	0	0	0
Myalgia	Any	1 (2)	5 (8)	6 (5)
	Severe	0	0	0
Arthralgia	Any	0	3 (5)	3 (2)
	Severe	0	0	0
Headache	Any	4 (6)	3 (5)	7 (5)
	Severe	0	0	0
Sweating	Any	0	3 (5)	3 (2)
	Severe	0	1 (2)	1 (1)
Fatigue	Any	1 (2)	2 (3)	3 (2)
	Severe	0	0	0
Fever (Temp. ≥ 38C)	Yes	0	1 (2)	1 (1)

Abbreviations: Temp., temperature; YOA, years of age.
Note: The numbers (N) in the header is the total number of subjects with documented reactions for fever (temp. ≥ 38°C).

Table 8 Overview of Unsolicited AEs – Safety Set

	Number (%) of Subjects With AEs		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N=66	**N=65**	**N=131**
Any AEs	4 (6)	5 (8)	9 (7)
At least possibly related AEs	4 (6)	4 (6)	8 (6)
SAEs	0	0	0
AEs leading to discontinuation	0	0	0
At least possibly related SAEs	0	0	0
Death	0	0	0

Abbreviations: AEs, adverse events; SAEs, serious adverse events; YOA, years of age.

Table 9 **Number (Percentages) of Subjects With Serious Adverse Events by Preferred Term Sorted by System Organ Class**

None reported.

Table 10 **Number (Percentages) of Subjects With Unsolicited Adverse Events Reported by > 5% of Subjects by Preferred Term sorted by System Organ Class**

None reported.

Conclusion:

In conclusion, the 2008/2009 AGRIPPAL® S1 influenza vaccine provides a very good immunogenicity and safety profile in adult and elderly subjects and complies with the Committee for Proprietary Medicinal Products (CPMP) criteria for approval of influenza vaccines.

Date of Clinical Trial Report: **23 JUL 08**